REMARKS

Claims 38, 41, 42, 44, 54, 55, 58, 59 and 61 are pending in the instant application. Claims 39, 49, 51, 52, 56, 57, 60 and 62-68 have been canceled, herein. Applicants reserve the right to pursue the subject matter of these claims in a continuing or divisional application. Claims 38, 44, 54, 55, 58 and 61 have been amended. Support for the amendments to claims 38 and 44 can be found, for example, in claim 54 as previously presented (generating a T-lymphocyte response), page 34, lines 9-18 and also in Figures 2 and 3 (T-lymphocyte mediated immune response against a herpes virus infection) of the instant specification. Support for the amendment to claim 54 can be found, for example, from page 10, line 26 to page 11, line 5 of the instant specification (immune response against infection) and claim 38 as previously presented (antigen). Support for the amendment to claims 55 and 61 can be found, for example, in claim 38 as previously presented. No new matter has been added.

Statement of Substance of Examiner's Interview

Applicant wishes to thank the Examiner for participating in an Interview with Applicant's counsel regarding the instant application on April 16, 2009. During the Interview, the Examiner, Supervisory Patent Examiner Robert Mondesi and Applicant discussed the claims of record, in particular claims 38 and 54.

Claim Rejections

Rejections under 35 U.S.C. § 103.

The Examiner has rejected claims 38, 39, 41, 42, 44, 49, 51, 52, and 54-64 under 35 U.S.C. § 103 as being anticipated by Williams *et al.* WO 97/02045 ("Williams") in view of Hazama *et al.* Immunology 78:643-649 (1993) ("Hazama"). Applicants have canceled claims 39, 49, 51, 52, 56, 57, 60 and 62-64 rendering this rejection moot as it applies to these claims. Applicants respectfully traverse.

The Examiner alleged that Williams teaches therapeutic agents of the treatment of mammalian diseases. The Examiner further alleged that Williams teaches that the pure B-subunit of *E. coli* heat labile enterotoxin (EtxB) binds to receptors found on the surface of mammalian cells and this binding induces differential immune response effects on lymphocytes

including activation of B and T cells. The Examiner further argued that Williams teaches the coadministration of EtxB with an antigenic determinant with each being administered as separate moieties. The Examiner further argued that Williams teaches that EtxB enhanced immune response and that EtxB caused increased B cell activation.

The Examiner also alleged that Hazama teaches that EtxB potentiates local IgA antibody response to co-administered antigens. The Examiner alleged that Hazama teaches immunization with Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (t-gD) with EtxB and that this combination exhibited high immunogenicity. The Examiner further alleged that glycoproteins of HSV are vaccines against HSV-1 infectious agents, based on the teachings of pages 33-37 of the instant specification. The Examiner alleged that Williams and Hazama teach the induction of a protective immune response against a Herpes virus and that the only difference between the claimed invention and the teachings of Williams and Hazama is the specific HSV antigen(s) selected. Applicants respectfully disagree.

First, Applicants argue that the Examiner has not provided a proper *prima facie* case of obviousness, because the teachings of Williams and Hazama do not teach each and every limitation of the claims and the Examiner has not explained why the differences between the claimed subject matter and the cited art are obvious. Second, the teachings of Williams and Hazama teach away from the claimed invention. Third, one of ordinary skill in the art would not have been motivated to combine the teachings of Williams with the teachings of Hazama.

No Prima Facie Case of Obviousness

Applicants submit that the combination of the teachings of Williams and Hazama do not teach the limitations of claims 38, 41, 42, 44, and 54, 55, 58, 59 and 61 and that the Examiner has not explained why the differences between the claimed subject matter and the teachings of the prior art are obvious.

Prior art is not limited just to the references being applied, but includes the understanding of one of ordinary skill in the art. The prior art reference need not teach or suggest all the claim limitations, however, *Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art.*[1]

The Examiner alleged, on the paragraph bridging pages 8-9 of the Office action that the specification teaches that HSV-1 glycoproteins are vaccines. The Examiner further alleged on

[1] MPEP § 2141 (emphasis added).

the bottom of page 9 of the Office action, that Hazama teaches the production of protective immunity against Herpes virus.

Applicants submit that while the instant specification teaches that HSV-1 antigens can act as vaccines against Herpes virus infection in combination with EtxB, it does not teach that each individual HSV-1 antigen will act as a vaccine against Herpes virus infection in combination with EtxB. Moreover, Hazama does not teach the production of a protective immune response through the administration of EtxB and t-gD. Rather, Hazama teaches that t-gD linked to EtxB failed to protect mice from viral infection.[2] That is, T-gD linked to EtxB caused a higher antibody titer than t-gD co-adminstered, but not linked with EtxB. Thus, if t-gD linked with EtxB have no protective immune response, t-gD co-administered but not linked with EtxB should not have produced such a response, either. Moreover, Hazama does not teach the co-administration of EtxB and a HSV-1 antigen produces a T-lymphocyte immune response. Hazama teaches that the reason that protective immunity was not induced was the lack of a T lymphocyte immune response in the absence of IL-2.[3]

Williams does not cure the deficiencies of Hazama. Williams does not teach the combination of EtxB and a HSV-1 antigen that acts as a vaccine, nor does it teach the induction of T lymphocyte immune response. Rather, Williams teaches that EtxB can be used as a vaccine carrier.[4] Williams teaches the use of EtxB as a vaccine carrier for the treatment of autoimmune disease[5] and for the treatment of T-lymphocyte leukemias.[6] This is because William teaches that EtxB induces apoptosis in $CD8^+$ T lymphocytes.[7] Hazama teaches that often, mucosally administered vaccines cause immune tolerance because of the induction of antigen specific suppressor T cells.[8] Thus, the combined teachings of Hazama and Williams teaches that EtxB produces co-administered with an antigen should produce immune tolerance and not a T lymphocyte immune response.

Williams and Hazama Teach Away from the Claimed Invention

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[2] *See* Hazama at page 647, second column, last paragraph and Table 4.
[3] *Id.* at page 648, first column, second full paragraph.
[4] *See* Williams at page 10, lines 9-13.
[5] *Id.* at page 2, lines 7-28 and page 3, lines 4-15.
[6] *Id.* from page 5, line 27 to page to page 6, line 11.
[7] *Id.* at page 2, lines 20-24.
[8] *See* Hazama at page 643, first column.

Applicants submit that the combination of the teachings of Williams and Hazama teach away from the invention of claims 38, 41, 42, 44, and 54, 55, 58, 59 and 61. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Applicants submit that Williams teaches that the combination of EtxB with antigen produces induction of tolerance through the induction of apoptosis of $CD8^+$ T cells. Hazama teaches that the induction of tolerance through down regulation of T cells leads to tolerance and ineffectiveness of a vaccine against Herpes virus. Hazama also teaches that the combination of EtxB with an HSV-1 antigen does not provide protective immunity. Thus, one of ordinary skill in the art would be discouraged from combining HSV-1 antigens with EtxB in order to enhance a T lymphocyte mediated or immunoglobulin mediated immune response against a herpes virus infection because no protective immunity was shown. Rather, the combination of Williams and Hazama teach that the combination of EtxB with any antigen, but specifically with t-gD induces immunotolerance.

No Motivation to Combine the Teachings of Williams and Hazama

Applicants also assert that one of ordinary skill in the art would not have had motivation to combine the teachings of Williams and Hazama. One of the requirements to make a *prima facie* case for obviousness is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.[9]

Williams teaches the induction of immune tolerance by co-administering EtxB with an antigen. Hazama teaches methods of forming an immune response to herpes virus by co-administering IL-2 and antigen. Hazama also teaches that the administration of EtxB with

[9] *See e.g.*, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Federal Register / Vol. 72, No. 195, Page 27528 / Wednesday, October 10, 2007.

antigen does not produce a T lymphocyte and thus does not confer protective immunity. One of ordinary skill in the art would not have combined the teachings of Williams with the teachings of Hazama to arrive at the invention of the instant claims. Neither Williams nor Hazama teach the effectiveness of induction of a T lymphocyte response by co-administering EtxB with an HSV-1 antigen. Indeed, both teach that this combination should induce immune tolerance as opposed to a T lymphocyte response. Thus, one of ordinary skill in the art would not be motivated to combine the teachings of Williams and Hazama.

For all of the above reasons, claims 38, 41, 42, 44, and 54, 55, 58, 59 and 61 are non-obvious over the teachings of Williams and Hazama and Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph.

The Examiner has also rejected claims 38, 39, 41, 42, 44, 49, 51 and 52 under 35 U.S.C. § 112, first paragraph, for lack of written description for adding new matter to the claims. The Examiner argues that there is no support for enhancing the leukocyte mediated immune response against an infectious disease. Applicants have canceled claims 39, 49, 51 and 52 rendering this rejection moot as it applies to these claims. Applicants respectfully traverse this rejection.

Applicants have amended claim 38, from which claims 41 and 42 to recite "generating a T-lymphocyte response". These elements are borrowed from claim 54, which was not rejected for lack of written description. The generation of a T-lymphocyte mediated immune response is supported in the specification at page 34, lines 9-18 and also in Figures 2 and 3. Figure 2 shows the generation of T cell proliferation, an indicator of a T-lymphocyte mediated immune response, in cells isolated from mice immunized with EtxB and HSV-1 antigen. Figure 3 shows similar results with mice immunized different combinations of doses of EtxB and HSV-1 antigen. Applicants submit that claims 38, 41 and 42 have sufficient written description and respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants submit that the claims as here amended put the application in condition for allowance, and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is invited and encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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